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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/657,006	DINGIVAN ET AL.	
	Examiner	Art Unit	
	ZACHARY SKELDING	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-82* is/are pending in the application.

4a) Of the above claim(s) *68,69,80 and 81* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-67,70-79 and 82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3-26-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of species filed November 13, 2007 is acknowledged.

   Claims 45-82 are pending.

   Applicant's election of "adult T cell leukemia" as the species of T cell malignancy to be treated and "a T cell malignancy refractory or non-responsive to chemotherapy" as the species of patient to be treated filed November 13, 2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

   Thus claims 45-67, 70-79 and 82 are under examination as they read on a method of treating a T cell malignancy comprising administering to a human in need thereof an effective amount of MEDI-507 or an antigen binding fragment thereof, wherein the species of T cell malignancy to be treated is "adult T cell leukemia"; the species of patient to be treated is one with "a T cell malignancy refractory or non-responsive to chemotherapy"; the species of anti-CD2 antibody is "MEDI-507" and "an anti-CD2 antibody with the proviso that said antibody is NOT MEDI-507 but it has the same properties as MEDI-507"; the species of experimental therapy is "aggressive combination chemotherapy"; the species of therapeutic agent or drug conjugated to antibody is "auristatin PHE" and the species of cancer therapeutic is "cyclophosphamide".

   Accordingly, claims 68, 69, 80 and 81 are withdrawn further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

2. This Office Action is in response to applicant's Amendment to the claims and Remarks filed July 18, 2007 as well as in response to applicant's election of species filed November 13, 2007.

   The previous substantive Office Action on the merits was mailed October 24, 2006.

   All previous rejections of record not repeated below have been withdrawn in view of applicant's cancellation of all previously pending claims and the addition of new claims 45-82 in the amendment filed March 26, 2007.

   New Grounds of Rejection are put forth below.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

   > The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 45-67, 70-79 and 82 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant argues that the terms "MEDI-507" and "Lo-CD2a/BTI-322 are definite in light of the disclosure of the instant specification.

Applicant's argument has been considered, but has not been found convincing, essentially for the reasons of record as put forth in the Office Action mailed October 24, 2006.

The instant claims are indefinite in the recitation of "MEDI-507" and "LO-CD2a/BTI-322" as the sole means of identifying these antibodies because these terms are merely laboratory designations which do not clearly define these antibodies. Different laboratories may use the same designations to define distinct biological materials.

Amending the claims to recite the appropriate ATCC Accession Numbers would obviate this rejection.

Applicant is reminded that any amendment to the claims must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 45-67, 70-79 and 82 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating tumors of T cell origin comprising administering to a human in need thereof an effective amount of an antibody that immunospecifically binds to human CD2 with the proviso that the antibody is not MEDI-507, or an antigen-binding fragment thereof, wherein the tumor of T cell origin comprises T cells that express CD2, does not reasonably provide enablement for a method of treating a T-cell malignancy comprising administering to a human in need thereof an effective amount of MEDI-507, or an antigen-binding fragment thereof, or an antibody that immunospecifically binds to human CD2 with the proviso that the antibody is not MEDI-507, or an antigen-binding fragment thereof, wherein the T-cell malignancy comprises cells that express CD2 and the T-cell malignancy is not a cutaneous T-cell lymphoma. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The disclosure of the specification does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states on page 1404, "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The instant claims, given their broadest reasonable interpretation consistent with the instant specification at page 11, penultimate paragraph, read on a method of treating any T cell malignancy comprising T cells that express CD2, including autoimmune diseases involving T cells and tumors where the T-cells expressing CD2 are part of the "malignancy" but are not necessarily the cells that originate the disease.

However, neither the disclosure of the instant specification, nor the knowledge in the art are sufficient for the skilled artisan to make and use the claimed invention to its full breadth.

While CD3 and CD4, like CD2, are known in the art to be widely expressed on both naive and activated T cells, the use of anti-CD3 and anti–CD4 antibodies to treat T cell malignancies such as multiple sclerosis has not been successful (see Wiendl et al., BioDrugs. 2002;16(3):183-200, in particular, page 196). Given the inability of anti-CD3 and anti–CD4 antibodies to treat multiple sclerosis, the skilled artisan would consider treating multiple sclerosis with yet another antibody that binds a widely expressed T cell antigen, anti-CD2 antibody, to be highly unpredictable.

Also, some malignancies, such as non-Hodgkin's lymphoma, occur in the lymph node. While 80-85% of non-Hodgkin's lymphomas are of B cell origin, and are thus characterized as B cell lymphomas, the lymph node containing these cancerous B cells also contains T cells that express CD2 (See, for example, Basic Pathology, 6th ed., Kumar, Cotran and Robbins eds., W.B. Saunders Co., pp. 362-369, 1997). However, the instant specification does not provide sufficient direction or guidance to treat non-Hodgkin's lymphomas of B cell origin by depleting the surroundings T cells.

In conclusion, the instant claims encompass an invention of tremendous breadth, and essentially call for trial and error by the skilled artisan to begin discovering how to use the claimed invention without assisting the skilled artisan in such an endeavor, which is insufficient to constitute adequate enablement.

The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Undue experimentation would be required to produce the invention commensurate with the breadth of the claims based on the disclosure of the instant specification and the knowledge in the art. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Moreover, it is apparent that the instantly claimed methods encompass the use of the "MEDI-507" and "LO-CD2a/BTI-322" antibodies in their breadth. As claimed elements, they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If they are not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the pertinent cell lines/hybridomas which produce these antibodies. See 37 CFR 1.801-1.809.

With respect to "LO-CD2a", Applicant argues the antibody is available from the ATCC as Accession No. HB11423.

Although this antibody may be available from the ATCC as Accession No. HB11423 and although U.S. Patent No. 5,730,979 indicates the deposit was made under the terms of the Budapest treaty, this does not necessarily mean that this antibody meets the requirements for enablement of a biological deposit in that it also must be true that the record of U.S. Patent No. 5,730,979 states that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent.

However, it is apparent from the U.S. Patent No. 5,730,979 records that the enablement requirements for the Lo-CD2a antibody under 35 U.S.C. § 112, 1st paragraph were satisfied. Therefore, Lo-CD2a is enabled for practice in the instant claims.

Applicant further argues that the amino acid sequence of MEDI-507 was available to one of skill in the art as of the effective date of the present application in Bazin Examples 11 and Figures 31 and 42, and that techniques for producing MEDI-507 are described in the instant specification. Thus, Applicant concludes the instant claims are enabled because one of skill in the art would have been able to obtain or make and use the "MEDI-507" antibody as claimed.

Applicant's argument has been considered but has not been found convincing, essentially for the reasons of record.

While Bazin discloses the sequence of the heavy and light chain variable regions of the "MEDI-507" antibody, it does not appear to disclose the sequence of the particular heavy and light chain constant regions found in the "MEDI-507" antibody.

Without the sequence of the complete antibody or a cell line encoding the antibody the skilled artisan could not make and use the claimed "MEDI-507" antibody, and thus, the instant claims are not enabled.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 45-54, 57-64, 66, 67, 70-79 and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dang (US 2003/0031665) in view of Shirono et al. (Blood. 1989 May 1;73(6):1664-71), Branco et al. (Transplantation. 1999 Nov 27;68(10):1588-96, cited on an IDS) and Bazin et al. (WO 99/03502, of record) and the instant specification at page 3, 1st paragraph.

Dang et al. (US 2003/0031665) teaches the treatment of cancer by administering an antibody that recognizes tumor cells (see Dang, in particular, page 1, paragraphs [0006]-[0007]. For example, Dang teaches the treatment of the aggressive T cell lymphoma known as adult T cell leukemia with anti-CD26 antibody (see Dang entire document, including the paragraph bridging pages 1-2, page 3, paragraph [0026] and [0031], and claims 15 and 34). Dang also teaches that while antibodies with intrinsic T cell depleting ability, such as an anti-CD26 antibody (see Dang, page 5, paragraph [0053] to page 7, paragraph [0072]), are useful therapeutically as unconjugated agents, conjugation of such an antibody to an additional therapeutic moiety, such as alkylating agent, can increase antibody effectiveness (see Dang, page 1, paragraph [0006], page 18, paragraph [0142] to page 19).

In addition, Dang teaches the concurrent administration of a targeted antibody based anti-cancer therapy with two or more additional therapeutic agents, including chemotherapeutic agents such as cyclophosphamide, so as to improve the efficacy of the therapy (see, in particular, page 2, paragraph [0013] and page 19, paragraph [0219], consistent with the art recognized principal of simultaneously administering several therapeutic agents each directed to different molecular targets so as to achieve additive-synergistic effects through the application of each agent at relatively low dose, thereby limiting the toxicity of each agent while increasing the total therapeutic effect.

The claimed invention differs from the reference teaching in that Dang does not explicitly teach the use of anti-CD2 antibody, in particular anti-CD2 antibody that competes with MEDI-507, at particular dosage and schedules of administration to treat adult T-cell leukemia.

However, it would have been obvious to use an anti-CD2 antibody as claimed to treat adult T cell leukemia (ATL) given the teachings of Shirono, Alberola-Ila and Bazin described below.

In particular, Shirono teaches that peripheral blood CD2 expressing T-cells obtained from several ATL patients exhibit greater CD2 immunofluorescence than do normal peripheral blood cells (see Shirono, in particular Figure 2). Shirono further teaches that the peripheral blood CD2 expressing T-cells obtained from several ATL patients also overexpress several T cell activation markers (see Shirono, in particular, Abstract and Introduction on page 1664 and Discussion on pages 1668-1670).

The teachings of Shirono that peripheral blood CD2 expressing T-cells obtained from several ATL patients appear to be activated and to express more CD2 than peripheral blood T cells obtained from non-cancerous individuals is consistent with the teachings of, for example, Alberola-Ila that activated peripheral blood T cells, i.e., TCR/CD3 activated T cells, express more CD2 than do naïve T cells (see, Alberola-Ila, in particular, Materials and Methods on pages 1085-1086 and Figures 2, 3 and 5).

Thus, it would have been obvious to one of ordinary skill in the art, given the teachings of Dang, Shirono and Alberola-Ila that an anti-CD2 antibody can be substituted for an anti-CD26 antibody to treat adult T cell leukemia.

Moreover, it would have been obvious to one of ordinary skill in the art, and one of ordinary skill in the art would have been motivated to use the anti-CD2 antibody MEDI-507 or an antibody that competes with MEDI-507 for binding to human CD2 to treat adult T cell leukemia given the teachings of Branco and Bazin.

More particularly, Branco teaches that MEDI-507 preferentially depletes activated T cells that overexpress CD2 (see Branco, in particular, page 1595, left column, 1st paragraph) and Bazin teaches a method for inhibiting the proliferation of T cells that express CD2 comprising administering a therapeutically effective amount of an antibody that immunospecifically binds to an epitope comprising amino acid residues 18, 55 or 59 of human CD2, with the proviso that said antibody is not MEDI-507 or LO-CD2a/BTI-322, for example an antibody that binds to the same epitope (or any part thereof) on human lymphocytes as the Lo-CD2a antibody (see Bazin, in particular page 1, 1st paragraph and page 12, 5th paragraph to page 13, 1st paragraph).

It is further noted that claims 76 and 77 recite administration of CD2 binding agent at a dose between 0.1-10 mg/kg/week, which given its broadest reasonable interpretation consistent with the instant specification, encompasses a unit dose of 8-800 mg/week based on an average weight of 80 kg (176 lbs) for the average human subject having cancer.

Bazin teaches the *in vivo* immunodepletion of $CD2^+$ lymphocytes with LO-CD2a/BTI-322, or an antibody that binds the same epitope or any part thereof, in humans, for example via the administration of 70 mg antibody over the course of a week, or in non-human primates (see

entire document, in particular page 38, 4th paragraph to page 39, 1st paragraph (human) and page 31, 5th paragraph to the paragraph bridging pages 36 and 37 and Figure 13 (non-human primates). Bazin also demonstrates the equivalent abilities of LO-CD2a/BTI-322 and MEDI-507 to immunodeplete $CD2^+$ lymphocytes in mice ((and page 89, 3rd paragraph to page 90).

Moreover, Bazin teaches that the LO-CD2a and MEDI-507 antibodies can be administered at an initial dose of at least 1 mg via intravenous infusion, and that higher or lower doses may be called for depending upon patient response.

Thus, according to the teaching of Bazin, the dosage and scheduling of administration of anti-CD2 antibody is an art recognized results-effective variable, i.e., a variable that is recognized as important for therapeutic use of anti-CD2 antibody and which therefore can be optimized by routine experimentation. See M.P.E.P. § 2144.05 II.B. and *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977).

While Bazin does not appear to explicitly teach the administration of MEDI-507 for six weeks or more as recited in claim 77, the scheduling of antibody administration is nonetheless obvious because it is a results-effective variable. "[w]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955), and see M.P.E.P. § 2144.05 II.A.

Moreover, it is well settled that "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." In re Boesch, 617 F.2d 272,276, 205 USPQ 215, 219 (CCPA 1980). See also Merck & Co. v. Biocraft Labs. Inc., 874 F.2d 804,809, 10 USPQ2d 1843, 1847-48 (Fed. Cir. 1989) (determination of suitable dosage amounts in diuretic compositions considered a matter of routine experimentation and therefore obvious).

Lastly, it should be noted that adult T cell leukemia is intrinsically a cancer "refractory or non-responsive to chemotherapy" as disclosed by the instant specification at page 3, 1st paragraph.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention.

9. Claims 45-54, 57-67, 70-79 and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dang (US 2003/0031665) in view of Shirono et al. (Blood. 1989 May 1;73(6):1664-71), Branco et al. (Transplantation. 1999 Nov 27;68(10):1588-96, cited on an IDS) and Bazin et al. (WO 99/03502, of record) as applied to claims 45-54, 57-64, 66, 67, 70-79 and 82 in Section 8 above, and further in view of Doronina et al. (USSN 09/845,786, of record).

The teachings of Dang, Shirono, Branco and Bazin are given in Section 8 above.

In addition, Dang teaches the use of antibody-toxin conjugates, a.k.a., immunotoxins, as a means to increase cancer cell killing of an anti-cancer cell antibody (see, in particular, page 1, paragraph [0006] and pages 13-14, paradgraphs [0142]-[0160]). More particularly, Dang teaches at page 13, paragraph [0146], that "[p]referred immunotoxins often include a plant-, fungal- or bacterial-derived toxin, such as an A chain toxin, a ribosome inactivating protein, α-sarcin, aspergillin, restirictocin, a ribonuclease, diphtheria toxin or pseudomonas exotoxin, to mention just a few examples. The use of toxin-antibody constructs is well known in the art of immunotoxins, as is their attachment to antibodies."

However, Dang does explicitly teach the use of the immunotoxin "auristatin PHE" in the preparation of an anti-cancer antibody conjugate.

Nevertheless, given that the anti-mitotic microtubule polymerization inhibitor "auristatin PHE" is another art recognized immunotoxin, and further given that Doronina teaches how to conjugate an antibody which binds to a cancer cell expressed polypeptide, e.g., CD30, to auristatin PHE, and further teaches how to use such an immunotoxin to kill cancer cells expressing the recognized antigen, e.g., a $CD30^+$ peripheral T cell lymphoma cell line (see Doronina, in particular, page 2, paragraphs [0024]-[0028]; page 23, paragraph [0302]; page 25, paragraphs [0322]-[0325] and page 34, example 19 and Figure 13B), it would have been prima facie obvious for one of ordinary skill in the art to prepare an anti-CD2-auristatin PHE immunotoxin that would possess a predictable ability to kill activated CD2-expressing T cells. See MPEP § 2144.06 and KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1742, 82 USPQ2d 1385, 1397 (2007).

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention.

10. Claims 45-64, 66, 67, 70-79 and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dang (US 2003/0031665) in view of Shirono et al. (Blood. 1989 May 1;73(6):1664-71), Branco et al. (Transplantation. 1999 Nov 27;68(10):1588-96, cited on an IDS) and Bazin et al. (WO 99/03502, of record) as applied to claims 45-54, 57-64, 66, 67, 70-79 and 82 in Section 8 above, and further in view of Taguchi et al. (J Acquir Immune Defic Syndr Hum Retrovirol. 1996 Jun 1;12(2):182-6).

The teachings of Dang, Shirono, Branco and Bazin are given above.

In addition, Dang teaches the concurrent administration of a targeted antibody based anti-cancer therapy with two or more additional therapeutic agents, including chemotherapeutic agents such as cyclophosphamide, so as to improve the efficacy of the therapy (see, in particular, page 2, paragraph [0013] and page 19, paragraph [0219], consistent with the art

recognized principal of simultaneously administering several therapeutic agents each directed to different molecular targets so as to achieve additive-synergistic effects through the application of each agent at relatively low dose, thereby limiting the toxicity of each agent while increasing the total therapeutic effect.

While, Dang does not explicitly teach the use of aggressive combination chemotherapy in the treatment of a T cell malignancy, Taguchi teaches an attempt to use aggressive combination chemotherapy which includes the chemotherapeutic agent cyclophosphamide, to treat a T cell malignancy refractory or non-responsive to chemotherapy, adult T cell leukemia (see Taguchi, in particular, Discussion pages 9-11 as renumbered by the Examiner).

Given the art recognized principal of simultaneously administering several therapeutic agents each directed to different molecular targets so as to achieve additive-synergistic effects through the application of each agent at relatively low dose, thereby limiting the toxicity of each agent while increasing the total therapeutic effect, it would have been obvious to one of ordinary skill in the art, and one of ordinary skill in the art would have been motivated to treat a T cell malignancy, such as adult T cell leukemia, with MEDI-507 or an antibody that competes with MEDI-507 in conjunction with aggressive combination chemotherapy, especially in light of the lack of success in the art of treating adult T cell leukemia with aggressive combination chemotherapy alone (see, e.g., Taguchi, in particular, Introduction on page 2 and Discussion pages 9-11 as renumbered by the Examiner).

It is noted that the phrase "aggressive combination chemotherapy" as recited in claims 55 and 56, given its broadest reasonable interpretation consistent with the instant specification, will be interpreted as encompassing the combination of two or more chemotherapeutic agents using a treatment regimen, i.e., dose and scheduling, as directed by a physician of ordinary skill in the art.

Also, it was prima facie obvious to employ in a method of treatment two compositions each of which is taught by prior art to be useful for same purpose the idea of combining them flowing logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention.

11. Claims 45-60, 66, 67, 70-79 and 82 are rejected under 35 U.S.C. § 103(a) as unpatentable over PR Newswire ("BioTransplant and Massachusetts General Hospital Announce Clinical Success In Transplant Protocol for Patients without Matched Donors", December 5, 2000), Borg et al. (Br J Haematol. 1996 Sep;94(4):713-5), Spitzer et al. (Blood, November 16, 2000, Vol. 96, No. 11 Part 1, pp. 841a, cited on an IDS) and Bazin et al. (WO 99/03502, of record).

PR Newswire teaches a method for treating blood cancers in patients with advanced refractory disease comprising administering non-myeloablative conditioning to the 60-70% of patients who do not have HLA-matched related donors wherein the conditioning regimen comprises less toxic chemotherapy and MEDI-507, followed by bone marrow transplantation.

The claimed invention differs from the reference teaching in that PR Newswire does not explicitly teach the use of the chemotherapeutic agent cyclophosphamide or the use of an antibody which competes with MEDI-507 for binding to CD2, or that the blood cancer being treated is a T-cell malignancy comprising cells that express CD2, or the dosage and means of administering anti-CD2 antibody, or that the T cell malignancy be adult T cell lymphoma.

However, it would have been obvious to one of ordinary skill in the art that any blood cancer, including a T cell malignancy of the blood, can be treated by making use of the method described in the PR newswire since, as is well known to one of ordinary skill in the art, the predominate means of treating blood cancer is via myeloablation followed by bone marrow transplantation.

For example, Borg teaches the treatment of adult T cell leukemia in a patient using aggressive combination chemotherapy followed by allogenic bone marrow transplant from an HLA-compatible sister (see, in particular, page 714, right column, 1st and 2nd paragraphs).

While the patient treated in Borg was HLA-compatible, 60-70% of patients do not have HLA-matched related donors as taught by PR Newswire and thus for those adult T cell leukemia patients one of ordinary skill in the art would be motivated to make use of the method taught by PR newswire as further described by the teachings of Spitzer and Bazin.

In particular, Spitzer teaches a method for treating hematopoeitc malignancies comprising administering a non-myeloablative conditioning regimen that comprises cyclophosphamide and MEDI-507, followed by bone marrow transplantation (see, in particular, Abstract).

Furthermore, Bazin teaches a method for inhibiting the proliferation of T cells comprising administering a therapeutically effective amount such as of MEDI-507 or antigen-binding fragment thereof or an antibody that immunospecifically binds to an epitope comprising amino acid residues 18, 55 or 59 of human CD2, with the proviso that said antibody is not MEDI-507 or LO-CD2a/BTI-322, for example an antibody that binds to the same epitope (or any part thereof) on human lymphocytes as the Lo-CD2a antibody (see entire document, in particular page 1, 1st paragraph and page 12, 5th paragraph to page 13, 1st paragraph).

Bazin teaches the *in vivo* immunodepletion of $CD2^+$ lymphocytes with LO-CD2a/BTI-322, or an antibody that binds the same epitope or any part thereof, in humans, for example via the administration of 70 mg antibody over the course of a week, or in non-human primates (see entire document, in particular page 38, 4th paragraph to page 39, 1st paragraph (human) and page 31, 5th paragraph to the paragraph bridging pages 36 and 37 and Figure 13 (non-human

primates). Bazin also demonstrates the equivalent abilities of LO-CD2a/BTI-322 and MEDI-507 to immunodeplete $CD2^+$ lymphocytes in mice (see, in particular, page 89, 3rd paragraph to page 90) and teaches that Lo-CD2a has been administered to patients to successfully treat GVHD (see, in particular, page 45, 1st paragraph).

Thus, given the successful use of MEDI-507 in a method of treating blood cancers according to the PR Newswire, it would have been obvious to substitute the art recognized equivalent antibodies that compete with MEDI-507 for binding to CD2 in such a method of treatment.

Moreover, it is further noted that claims 76 and 77 recite administration of CD2 binding agent at a dose between 0.1-10 mg/kg/week, which given its broadest reasonable interpretation consistent with the instant specification, encompasses a unit of dose of 8-800 mg/week based on an average weight of 80 kg (176 lbs) for the average human subject having cancer.

However, Bazin teaches the *in vivo* immunodepletion of $CD2^+$ lymphocytes with LO-CD2a/BTI-322, or an antibody that binds the same epitope or any part thereof, in humans, for example via the administration of 70 mg antibody over the course of a week, or in non-human primates (see entire document, in particular page 38, 4th paragraph to page 39, 1st paragraph (human) and page 31, 5th paragraph to the paragraph bridging pages 36 and 37 and Figure 13 (non-human primates). Bazin also demonstrates the equivalent abilities of LO-CD2a/BTI-322 and MEDI-507 to immunodeplete $CD2^+$ lymphocytes in mice ((and page 89, 3rd paragraph to page 90).

Moreover, Bazin teaches that the LO-CD2a and MEDI-507 antibodies can be administered at an initial dose of at least 1 mg via intravenous infusion, and that higher or lower doses may be called for depending upon patient response.

Thus, according to the teaching of Bazin, the dosage and scheduling of administration of anti-CD2 antibody is an art recognized results-effective variable, i.e., a variable that is recognized as important for therapeutic use of anti-CD2 antibody and which therefore can be optimized by routine experimentation. See M.P.E.P. § 2144.05 II.B. and *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977).

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention.

12. No claim is allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZACHARY SKELDING whose telephone number is (571)272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Zachary Skelding, Ph.D.
Patent Examiner
February 17, 2008

/Michail A Belyavskyi/
Primary Examiner, Art Unit 1644